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Histomorphometric analysis of intrapulmonary vessels in patients undergoing bidirectional Glenn shunt and total cavopulmonary connection

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Objectives: The purposes of this study were to elucidate the histomorphometry of the intrapulmonary arteries in patients undergoing univentricular type of repairs and to identify the histomorphometric characteristics, if any, that may predispose patients to postoperative Fontan failure.

Patients and methods: Operatively resected wedges of lung tissue from 44 patients undergoing univentricular type of repairs (aged 17 months to 34 years; mean, 83.52 ± 75.90 months) was subjected to histomorphometric analysis.

Results: Despite pulmonary arterioplasty, a low Nakata index was associated with 9.61 (95% confidence interval: 1.01–91.5; $P = .003$) times increased risk of death after the operation. A statistically significant difference in the mean indexed diameter of the intra-acinar pulmonary arteries ($P = .03$) was observed between patients undergoing superior and total cavopulmonary connections. Overall, there were 8 (8.2%), 4 (9.1%), 13 (29.5%), and 29 (65.9%) instances of intrapulmonary arterial intimal lesions, thrombosis, smooth muscle extension, and interstitial fibrosis, respectively. Among patients undergoing total cavopulmonary connection, only low Nakata index was significantly associated with the presence of severe intimal lesions, abnormal smooth muscle extension, intra-acinar pulmonary arterial thrombus, and smaller intra-acinar pulmonary arteries.

Conclusions: A low Nakata index is significantly associated with the presence of severe intimal lesions, thrombus, abnormal smooth muscle extension, a lower mean indexed area of the intrapulmonary arteries, and poor postoperative outcome. However, none of the histomorphometrically derived parameters could conclusively predict the outcome after univentricular repair. (J Thorac Cardiovasc Surg 2010;140:1251-6)

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Despite fulfilling the indications based on hemodynamic data, systemic ventricular mass, pulmonary artery (PA) size with an unobstructed, unrestricted Fontan pathway, and a fenestrated atrial baffle, a subset of patients in the postoperative period has low cardiac output and marked accumulation of extracellular fluid resistant to medical treatment and dies owing to elevation of pulmonary vascular resistance (PVR) and ventricular failure.[E1-E7]

It is widely known to clinicians that in patients undergoing the univentricular type of repairs with borderline Nakata index, the intrapericardial PAs can always be surgically augmented to the desired width and PVR is determined in the peripheral vascular bed, well beyond the surgeon's reach.[E8] Autopsy studies have suggested that in patients undergoing univentricular repair, intra-PA structure cannot always be inferred from the preoperative hemodynamic data. Medial hypertrophy and/or decreased intra-PA concentration have been reported to exist in these patients with normal PA pressure and PVR.[E9-E14]

On the basis of these observations, we hypothesized that in the presence of an unrestricted Fontan pathway, these microvascular changes could be the contributing factor for high PVR in the postoperative period. However, histopathologic or ultrastructural studies of the lung tissue to lend credence to this hypothesis have been limited and controversial because of limited number of patients and restricted observations.[E1-3,E9-E11] Second, patients who had died because of definite technical problems were not excluded from analysis of outcome.[E1-E4,E12-E15]

With this background, we conducted this study (1) to elucidate the histopathology and morphometry of the intrapulmonary vessels of patients undergoing the univentricular-type of repair (ie, superior cavopulmonary connection [SCPC]) and total cavopulmonary connection [TCPC]); (2) to identify the relationship, if any, between the histomorphometry and

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Abbreviations and Acronyms

CI = confidence interval
PA = pulmonary artery (arterial)
PAP = pulmonary artery pressure
PVR = pulmonary vascular disease
Sao_2 = systemic arterial oxygen saturation
SCPC = superior cavopulmonary connection
SVEDP = systemic ventricular end-diastolic pressure
TCPC = total cavopulmonary connection

preoperative hemodynamic parameters; (3) to identify the relationship of intra-PA structure to postoperative outcome; and (4) finally, to determine whether histologic criteria of the intrapulmonary vasculature could be established in decision-making for appropriate selection of patients for univentricular repairs.

PATIENTS AND METHODS

Criteria for Patient Selection

Selection criteria for 1-stage univentricular repair. In this study, patients with a functionally univentricular heart and satisfying the following standard prescribed criteria underwent 1-stage univentricular repair:

1. Satisfactory PA size (preoperatively and intraoperatively measured PA size with a Z-value > –2, McGoon ratio > 2.0, and/or Nakata index > 250 mm · m^{-2})
2. Mean PA pressure less than 15 mm Hg or more than 20 mm Hg with a net left-to-right shunt
3. An indexed PVR less than 3.0 Wood units/m^2 and a preoperative Mayo index less than 4.0
4. Satisfactory systemic ventricular function (end-diastolic pressure [(SVEDP] ≤ 12 mm Hg, systemic ventricular ejection fraction ≥ 0.35)
5. No significant systemic ventricular hypertrophy (assessed by systemic ventricular mass and/or systemic ventricular posterior wall thickness) with a Z-value of less than –4.0
6. No left ventricular outflow obstruction (echocardiographically, a cross-sectional area of the bulboventricular foramen or ventricular septal defect > 2.0 cm^2 · m^{-2})
7. No more than mild aortic or left atrioventricular valve regurgitation

Subsequently, these patients were grouped according to Texas Heart Institute Fontan Risk score.[E16] Patients with a score of 0 to 3 were considered to be at low risk for a Fontan operation, those with a score of 4 to 5 were considered to be at moderate risk, and those with a score of 6 or more or with a score of 3 in any single category of Texas Risk score were subjected to SCPC as an interim palliation.

Selection criteria for extracardiac Fontan procedure. On the basis of our early experience, extracardiac TCPC was performed in patients with (1) age older than 3 years, (2) body weight of 10 kg or more, (3) anomalies of systemic and pulmonary venous return, (4) auricular juxtaposition, (5) completion Fontan after a previous SCPC connection, and (6) no requirement for additional intracardiac procedures.[E7]

Conduct of the Study

Patients were enrolled for this prospective study after institutional ethics committee approval and informed written consent from parents/guardians. Between January 2006 and July 2009, specimens of excised lung tissue from 50 consecutive patients undergoing either SCPC or TCPC at our institute were subjected to histopathologic and morphometric analysis. Of these, 44 samples from 44 patients (32 male subjects) were found suitable for analysis (6 were excluded because of morphologic artifacts resulting from inadequate fixation and/or poor orientation). The examiners were blind to demographic and clinical data including hemodynamic and operative data.

Age at operation was 17 months to 34 years (mean 83.52 ± 75.90 months) with 77.3% (n = 34) of patients being younger than 48 months of age. Cardiac catheterization and angiocardiography were performed on all patients to confirm the diagnosis, to define PA anatomy, to measure PA pressure (PAP), and to identify major aortopulmonary collateral arteries (E-Appendix 1).

Twenty-nine (65.9%) patients had tricuspid atresia, and the remaining 15 (34.1%) patients had complex cyanotic congenital heart diseases with a functionally univentricular heart. Eight (18.2%) patients had right atrial isomerism. Twenty-one (47.8%) patients had various palliative procedures before univentricular repair. Four patients had bilateral superior venae cavae. Patients with moderate or severe atrioventricular valve regurgitation (n = 2) underwent lateral tunnel TCPC with concomitant atrioventricular valve repair. Descriptive characteristics, underlying cardiac diagnoses, and the relevant cardiac catheterization data are summarized in Table E1.

Hemoglobin value ranged from 11 to 24 g/dL and systemic arterial oxygen saturation (Sao_2) was 65% to 91%. Mean PAP or pulmonary capillary wedge pressure ranged between 12 and 18 mm Hg (mean ± SD = 14.25 ± 1.78 mm Hg) and mean SVEDP ranged between 10 and 16 mm Hg.

In 3 patients with severe pulmonary stenosis and deep cyanosis, pulmonary venous wedge pressure was used as a substitute for PAP for calculation of PVR at preoperative cardiac catheterization. PA size measured intraoperatively with a Hegar dilator was compared with the anticipated confidence limits for age and body surface area, and a 1-stage univentricular repair was carried out as per the selection criteria. A localized PA narrowing reducing adjacent PA diameter by 50% or more before its branching was an indication for pulmonary arterioplasty.

All patients were operated on with cardiopulmonary bypass using aorta–bicaval cannulation and moderate systemic hypothermia. The ligamentum arteriosum or persistent ductus arteriosus was divided in all cases, the Blalock–Taussig shunt was divided (n = 17), and unilateral (n = 40) or bilateral (n = 4) SCPC was performed. The SCPC was carried out on a beating perfused heart. Antegrade cold blood cardioplegia was used for myocardial protection and was repeated every 30 minutes to complete the Fontan connection in 13 patients.

Total extracardiac right heart bypass was accomplished with a polytetrafluoroethylene conduit on a beating, perfused heart without cardioplegia. Size of the conduit and weight distribution of the patients were as follows: polytetrafluoroethylene conduit 18 mm: 1 patient, 16 kg; 20 mm: 1 patient, 24 kg.

After completion of the surgical procedure and disconnection of the patient from cardiopulmonary bypass, lung biopsy tissue from the lower lobe of the right lung (n = 39) was obtained through a small pleural opening. In patients with a previous Glenn shunt, a biopsy specimen was taken from the lower lobe of the left lung (n = 5). A Cooley vascular clamp was applied and a small portion of the lung tissue (1.0 × 0.5 cm) was excised for histopathologic examination. The raw margin was sutured in 2 layers. The pleural cavity was closed in all cases. No complications related to lung biopsy, such as pneumothorax or bleeding, were observed in any of the cases.

Analysis of Lung Tissue

Each lung biopsy specimen was analyzed by 2 pathologists independently without any knowledge of demographic, hemodynamic, and operative data. At least 20 intra-acinar small PAs having a diameter greater than 100 μm were examined for histomorphometric studies. There was no interobserver disagreement on the interpretation of the presence or absence of disease.